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A randomised trial to compare the performance of Oxyzyme® & Iodozyme® with standard care in the treatment of patients with venous and mixed venous/arterial ulceration

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Abstract

This study was to evaluate the potential benefits of two products (Oxyzyme® & Iodozyme®) into a leg ulcer service in South Staffordshire, UK.

A randomised controlled Trial (RCT) was used to evaluate time to ulcer healing, quality of life, pain and cost effectiveness.

100 patients were randomised to receive either Oxyzyme/ Iodozyme (active group) or standard care (control group) with venous or mixed arterio-venous ulcers. Patients were evaluated weekly up to 12 weeks, with further follow up at 24 weeks. Whilst there was a small benefit in terms of healing over follow up using the Cox Proportional Hazards Model, this did not achieve a standard level of statistical significance (Hazard Ratio= 1.13, 95%CI 0.64 to 2.02, p=0.67) after adjustment for confounding factors. Patients with high protease activity showed an improved and faster healing in the active group, (HR=1.35, 95%CI 0.63, 2.87)p=0.44.

The active group required significantly fewer dressing changes (14.8 versus 10.0, p=0.033). Despite the dressing costs being higher, there was a significantly lower cost of nursing time, leading to a greater cost effectiveness in terms of cost per healed ulcer (£977 versus £1071. A Markov model used to assess cost effectiveness in the main trial found that the control group had slightly better outcomes (12 more ulcer free weeks), but at a substantially greater cost (£5,031). When those with high protease activity the cost in the active group dominated, with lower cost (-£2,450) and an improved outcome (29 more ulcer free weeks).

Health related quality of life (HRQoL) and pain significantly improved over the assessment period, though there was no difference between the treatment groups.

The use of Oxyzyme® & Iodozyme®) could provide better value for money in the management of venous and mixed arterio-venous ulcers than standard care in a community leg ulcer service.

Introduction

Leg ulceration remains a major health care problem affecting over 100,000 people at any one time in the UK [1]. Despite advances in the delivery of care and improvements in assessment and treatment with compression many patients experience protracted periods of time unhealed causing significant impact on their quality of life. In addition to the personal cost this is a large drain on health care resources at a time of pressure on resources in the NHS [2].

Traditional approaches to treatment of venous and mixed ulceration have focused on the application of compression as the most important component of treatment [3,4]. Relatively little attention has been placed on understanding how manipulation of the wound environment may enhance healing, particularly when wounds have become chronic. New products are emerging that could transform this situation and promote healing by controlling and optimising the micro-environment of the wound cavity. However these products must be evaluated to demonstrate their potential benefit in terms of clinical and cost effectiveness [5].

An adequate supply of oxygen has long been recognised as key to successful wound healing. Until recently approaches to avoiding a restrictive hypoxia in wounds have relied on systemic approaches such as hyperbaric oxygen or inhaled oxygen [6,7] The new dressings evaluated in this study represent a clinical development in this area through the development of new, active hydrogel dressings that incorporate an enzyme system intended to optimise the conditions within the wound bed. Whilst the system undertakes a programmed production of iodine, the pH is optimised by the generation of gluconate and the oxygen balance is restored as a consequence of another by-product in the form of dissolved oxygen at the interface between the wound and dressing. The overall effects of the micro-environmental optimisation (including moisture control) become apparent at the visual clinical level (through continued use) as enhanced autolytic debridement, healthy granulation and orderly epithelisation.

A variety of enzymes are deployed by the cells present in and around the wound with which to break down the matrix in a controlled manner, as an essential part of the tissue re-modelling that is the basis of active healing. Matrix Metalloproteinases are prominent components of this set, and they fulfil a central role in the processes of healing, as well as in normal tissue homeostasis. As part

and parcel of these regenerative and maintenance procedures, blood vessels that deliver oxygen and nutrients to the new tissue must undergo radical modification. Building of new blood vessels (angiogenesis) is particularly dependent on the activity of MMPs to clear away damaged extra cellular matrix in order to make space for the new microvascular structures required to sustain the new tissues.

The role of MMPs in wound healing is so complex that diagnostic opportunities based on measurements of MMP concentration or activity are only just becoming possible. In humans there are at least 24 different MMPs with varying roles and produced in a variety of cell types. This family of enzymes is involved in complex multiple molecular interactions and biochemical pathways with other proteinases and substrates.

The Oxyzyme® dressing (Archimed, Knutsford UK) being evaluated in this study has been developed to provide a new level of support to the process of wound healing. At the same time as impeding microbial growth, it optimises the environment of the wound bed for favourable biochemical and cellular processes. The dressing contains glucose oxidase to make hydrogen peroxide and a halide, iodide, to make hypoiodite (similar to hypochlorite) which leads to iodine. When the dressing is removed from its airtight package and the two layers are brought into contact with each other, the oxidase enzyme within the top layer is ready to start its reaction with oxygen. Just as leukocytes activate their oxidase enzyme to generate hydrogen peroxide, so the assembled 2-layer dressing uses oxygen from the air to produce a steady flow of hydrogen peroxide in the dressing. While the dressing is in contact with the wound surface, the hydrogen peroxide is converted to water and dissolved oxygen by serum catalase in the wound. The wound bed becomes rich in locally available oxygen, with all of its associated benefits, to work in harmony with the antimicrobial effects of the iodine and the various other optimising effects of the dressing.

Iodozyme® (Archimed, Knusford, UK) is a sister product to Oxyzme® and has been developed for patients who are considered to have particular problems with chronic infection or bacterial burden. It is based on the same dressing characteristics and differs only in the amount of iodine produced and the absorptive capacity of the wound contact gel. The assembled dressing ready for use comprises a two layer, composite hydrogel. As with Oxyzyme, it absorbs wound fluid while the gel conforms to the wound bed, maintaining an optimised moist environment. The level

of iodine produced in the dressing is substantially higher than produced by the Oxyzyme product. However, both dressings have lower levels of Iodine compared with other Iodine based dressings, but have similar antimicrobial properties.

The aim of this trial was to examine the relative clinical and cost effectiveness of using these complex dressings in the healing of venous and mixed venous and arterial ulceration within a well- established wound care service.

The aim of the sub-protocol in this trial was to determine whether the use of the Oxyzyme® and Iodozyme® dressings modulate the levels of metalloproteinases, and from this to determine whether such a modification is influencing healing in patients with high initial levels of these enzymes. Details of this study will be published elsewhere.

Patients and Methods

The study was a prospective, randomised, parallel groups, open study to compare the use of a new dressing regimen Oxyzyme/Iodozyme (active group) with standard treatment (control group) for leg ulceration in the healing of venous and mixed venous/ arterial ulceration.

Primary objective:

- The main objective was to determine the relative effectiveness of introducing the trial products compared with standard care. Effectiveness was defined as complete ulcer closure on the reference ulcerated limb (100% re-epithelialization) at 12 weeks or before if this occurred.

Secondary objectives:

- To determine which was the most cost effective treatment in ulcer healing.
- To determine which wounds benefitted most from the intervention
- To determine whether pain improved with treatment.
- To determine which treatment gave the best patient outcome in terms of health related quality of life (HRQoL)
- To examine adverse events associated with treatment.

- To determine longer treatment follow up in patients with harder to heal ulcers (to 24 weeks).

This study was designed as a preliminary study to evaluate the potential benefit of these advanced wound therapies in healing patients with chronic leg ulceration. A sample size of 100 was selected, though this was not based on a formal power calculation as no previous studies had been undertaken to allow for this calculation. It was anticipated that a sample of 100 patients would provide insight into the future potential of the treatment and allow for more precise power calculations in further studies.

Patients were drawn from the South Staffordshire PCT Tissue Viability Service. All patients within the service who met the inclusion criteria were considered for this trial. Patients who newly presented for treatment within the clinical areas of the Trust were also considered for entry during the study period.

The following criteria had to be met before a patient was recruited to the trial.

Inclusion Criteria

Age:	At least 18 years of age.
Gender:	Males Females - provided they were not pregnant or breastfeeding
Presentation:	Patients with a venous ulcer (ABPI defined as >0.8) **or** Patients with a mixed ulcer (venous ulcer with mild concurrent peripheral arterial disease (ABPI greater than 0.6)
Diagnosis:	Patients with ankle brachial pressure index (ABPI) ≥0.8 were considered to have minimal arterial disease using a standard procedure.

A diagnosis of venous disease was established through clinical criteria for chronic venous insufficiency. This included the presence of varicose veins, evidence of liopodermatosclerosis, varicose eczema and ulceration in the ankle and lower calf

area. Previous history of deep vein thrombosis and varicose vein treatment were also used as part of the criteria.

Patients with mixed venous disease with mild peripheral arterial disease were classified according to the level of the ankle to brachial pressure index. An ABPI > 0.8 was considered safe for high compression (40 mmHg at the ankle) with minimal peripheral arterial occlusive disease present. An ulcerated limb with an ABPI of between 0.6 and 0.8 was considered to have a mixed arterial-venous aetiology and was treated with a lower level of compression (<25mmHg).

Wound characteristics included mild or moderate levels of exudate, with an ulcer size between 2 and 50 cm^2. The wound had to present for less than one year, with healthy peri-wound skin. Only patients who were willing and able to give written informed consent were eligible for inclusion in the trial.

Exclusion Criteria

Specific exclusions included severe peripheral arterial occlusive disease defined as an ABPI of < 0.6 in whom it is unsafe to receive compression. Patients had to be able to tolerate the correct level of compression for their clinical condition. Patients who experienced an acute deep vein thrombosis within the last 3 months, or who had undergone surgery for chronic venous insufficiency in the last 2 months were also excluded, as were patients who had undergone arterial reconstruction or angioplasty for peripheral arterial occlusive disease in the last 3 months.

Patients with a clinically defined active cellulitis which was being treated using systemic antibiotics at the start of the trial were excluded. However, should cellulitis develop during the trial they did not need to be withdrawn. This was however, noted as an adverse events.

Patients receiving treatment for thyroid disorders including treatment with thyroxine and Iodine and those on lithium carbonate were also excluded. Patients with a known hypersensitivity to one of the components of the new dressings and those with peri-wound maceration or uncontrolled varicose eczema around the ulceration were not included. Finally, patients confined to bed and pregnant or breastfeeding were excluded from the trial.

Patient Recruitment

The clinical investigator identified eligible patients according to the selection criteria and an agreed checklist. Patients were questioned on their previous medical history and their limb and ulcer were examined. All patients who did not fit the entry requirements for the trial were excluded. Before being admitted to the clinical study, the patient consented to participate, after the nature, scope and possible consequences of the study had been explained in an understandable form. The patient's GP was informed of their participation.

Randomisation

The Clinical Nurse Specialist held the randomisation envelopes. Randomisation took place following the eligibility check and after obtaining the patient's written informed consent. To assure equality of groups the randomisation was stratified according to whether the patient had pure venous or mixed aetiology ulceration. Randomisation was performed by opening an envelope containing the patient's trial number and details of the treatment to be applied after eligibility criteria had been met and written consent had been given.

Patients with bilateral leg ulceration were randomised to one dressing system that was used on both limbs. The study limb was taken as the limb which had the largest area of ulceration on wound measurement.

In total there were two patient groups

Group I (Active): patients receiving Oxyzyme/ Iodozyme (in conjunction with compression therapy based on formulary recommendations for the Service),

Group II (Control): patients receiving standard care (continuation with current treatment regimen including compression therapy based on formulary recommendations for the Service).

Clinical Measures:

The main clinical outcome was complete ulcer closure on the reference limb (100% re-epithelialization) at 12 weeks or before if this occurred.

At the initial assessment the patient's ulcer was drawn using acetate and pen and the wound area was estimated by planimetry. The wound area was re-measured at each weekly assessment visit although the wound might have been redressed more frequently between these visits.

Non invasive investigation using Doppler Ultrasound was used to confirm the arterial status of the patient's leg using Ankle Brachial Pressure Index (ABPI) measurement. Other assessments made during their initial assessment included:

- History of ulceration
- Relevant medical history
- Pain assessment using the VAS from the McGill Pain questionnaire
- Health related quality of life – This was repeated at 12 weeks or earlier if the wound healed before this time. A final assessment of quality of life was made at 24 weeks on all patients, both healed and unhealed.

Treatment interventions.

For all included patients the scheduled treatment duration was 12 weeks. Patients were allocated through a process of randomisation to either active or control treatment based on the local wound care formulary.

The dressings were applied according to manufacturer's instructions and local agreed policy. The investigator was responsible for ensuring that all clinical staff were familiar with the new dressings being studied and that the application and removal methods were adhered to. In addition, all other treatments used conformed to the agreed local wound formulary that supports decision making in this service. Wound swabs were taken at each weekly dressing change to examine the levls of MMP activity using a standardised proprietary test (Reverse ELTABA, Mologic Limited, Bedford, UK).

Because of the variability of the different wounds some patients required more frequent dressing renewal according to clinical need. Typical reasons for increasing the frequency of dressing change included heavy exudate or wounds with a large surface area. Extra dressing changes by health professionals were recorded in the case report form (CRF) as appropriate. Patients who suffered from bilateral

ulceration received the trial products on both limbs provided that the wounds on the other limb were suitable to receive the dressings.

Use of secondary dressings

Oxyzyme® and Iodozyme® were applied to the wound bed as primary dressings and required a secondary dressing to secure them in place. In order to allow the dressings to generate oxygen and iodine, a breathable secondary dressing was selected. The level of exudate from the wound guided the selection of secondary dressing based on the criteria below. All of these dressings were included within the wound care formulary.

Exudate level	**Dressing choice**	**Rationale**
Low exudate level	Film dressing	Retain the moisture within the primary dressing and avoid from drying out
Low / medium level	Surgipad/thin foam	Allow moisture evaporation through the vapour permeable outer layer of the secondary dressing

Application of compression

Patients with venous ulceration were treated with high compression therapy using the wound care formulary recommendations which follow national guidelines and best available evidence. Systems of high compression used were multi-layer which are designed to apply a resting pressure of approximately 40mmHg.

Patients with a level of concurrent peripheral arterial disease were treated with reduced compression bandage systems that aimed to apply a pressure not greater than 25mmHg.

Patients whose ulcer healed during the study were fitted with appropriate compression hosiery to help reduce the risk of ulcer recurrence.

Patients were seen every 1 week ± 3 days until the 12th week for wound assessment, with all the visits being documented in the case report form (CRF). Patients were not assessed between the 12th assessment visit and week 24. A

final evaluation of the ulcer status was undertaken at week 24 with the health related quality of life assessment.

At each visit the investigator performed a clinical assessment of the wound according to a standard protocol, and assessed the size of the wound.

Between the weekly scheduled visits, every dressing and compression system change was documented by the investigator in an appropriate form. At each dressing change, the primary and secondary wound dressing was changed as well as the compression.

The treatment was stopped, temporarily or permanently, before the required 12 weeks had been completed if the investigator deemed this to be necessary. This was then documented in the case report form. A temporary discontinuation of the allocated treatment system did not exceed 2 weeks. After this time, it was assumed to be a permanent discontinuation.

Patient's Quality of Life

Quality of life was assessed using a validated tool (VLU-QOL) [8]. This gives scores in three domains, namely activities; psychological and symptom distress. Each score is transformed to give a score from zero (perfect health) to 100 (worst possible health). Thus, any reduction in VLU-QOL score is indicative of an improvement in health related quality of life. The visual analogue (VA) scale for perceived pain was taken from the McGill short form pain scale (9).

The patient's quality of life was assessed at baseline and at the end of the treatment period (Week 12 or at the end of the tested dressing treatment, whatever the reason) and at 24 weeks in accordance with a standard protocol.

The investigator was responsible for identifying adverse events that occurred to each participant throughout the study. An adverse event could occur at any time during the conduct of the study, in any phase of the study or after the study was completed. An adverse event could have been identified by the investigator or reported by the participant.

Cost Effectiveness Analysis

The cost information was collected at each weekly visit for both groups. This included information on bandages and dressings used together with the number of applications within that week. Information on bandage and dressing usage during the interim visits was collected to confirm that the management of patients did not differ between the weekly visits and interim visits. Information on the unit cost of dressings and bandages was based on the British National Formulary [10] which was accessed during the analysis phase of the study from September 2012 to November 2012. Nurse time was estimated at 27 minutes contact time based on previous studies and information collected on treatment changes during the present study. The cost of a visit was estimated as £27 per visit based on PSSRU 2011 data [11]. Hosiery costs were assumed to be zero as these were not renewed at dressing changes, but rewashed. Hosiery was also used to maintain the healed ulcer.

Cost effectiveness was determined in two ways. Firstly the total cost of care was determined in the two groups during the active treatment phase of the trial up to complete healing, withdrawal or reaching 12 weeks of treatment. A cost per healed ulcer was then calculated based on this information.

Secondly a Markov chain analysis was used to examine the costs and healing over time to determine whether this led to a more cost effective approach. The Markov method is well established in health economic analysis. It is based on the patients being in a variety of health states at weekly intervals during their treatment. For the purposes of this study the health states were given as:

1. On randomised treatment: patients receiving the randomised treatment.
2. Withdrawal from treatment. In patients who withdrew this health state was assumed to be for a two week period.
3. Off study treatment. This was assumed to occur after the two weeks withdrawal period where patients were still being treated up to 12 week cut-off.
4. Healed. Patients were assumed not to require leg ulcer treatment and as such no cost was associated with this health state.

Information on how long each patient was in each health state were collated and costs for each health state were determined from the trial data. Effectiveness was estimated by determining the number of ulcer free weeks for the two randomised groups and estimating the Incremental cost effectiveness ratio (ICER) as follows:

ICER= Cost of treatment (Control) - Cost treatment (Active)
Ulcer free weeks (Control) – Ulcer free weeks (Active)

Trial Monitoring

The Trial Monitor telephoned and visited the centre at appropriate intervals to check on the progress of the evaluation, compliance with the protocol and to ensure the acceptability of the data. The on-site checking of the case record forms for completeness and clarity, spot-checks and cross-checks with source documents (giving due consideration to data protection and medical confidentiality) were carried out by the trial monitor.

Before the start of the study the protocol was submitted to Leeds West Research Ethics Committee (REC) for approval. In addition the research was registered with the R&D office of the trust.

Analysis

Data were entered on to an ACCESS database designed for the trial. All analysis was undertaken using the Stata 11.0 statistical package.

All patients with at least one follow up visit were included in the analysis according to the randomised treatment. Principal analysis was on an “intention to treat” basis, namely according to what the patient was randomised to, irrespective of their actual treatment.

Baseline Data

The baseline data were summarised using descriptive statistics by treatment group and overall. Where baseline data were collected on each limb, this was summarised by trial limb.

The principal endpoint was complete ulcer closure (100% epithelialisation) following twelve weeks of treatment. This was undertaken using Kaplan Meier plots, with

statistical analysis using the Cox Proportional Hazards model which was used to determine the influence of confounding factors on this outcome.

The quality of life data were analysed using a repeated measures mixed model using the REML method.

Cost effectiveness analysis used a Markov model to determine the outcomes of treatment (ulcer free period) in relation to the cost of care and from this to estimate the cost effectiveness ratio.

Results

In total 100 patients were entered into the trial and randomised between February 2011 and January 2012. Figure 1 gives the trial flow diagram. Table 1 gives details of the patients in terms of their basic demography and selected allied health problems.

Baseline Information

In total 53 patients were randomised to a control dressing and 47 were randomised to the active group). The average age of the participants was 69.5 years, with similar distribution of ages between the two randomised groups. There was a roughly even split between men and women, with slightly fewer men in the active group. The groups were reasonably well matched for the selected health problems, with slightly more patients with hypertension and rheumatoid arthritis in the control group.

Table 2 gives details of the venous and cardiovascular signs in the two arms of the trial. Patients in the active group had slightly more signs of venous disease (varicose veins and venous surgery), though slightly fewer with history of myocardial infarction and arterial leg surgery. No patients had a history of diabetic foot ulceration.

Leg ulcer details are given in table 3. Again, the randomised groups were reasonably matched. Ulcer duration was on average 18 months, though this varied from one week to 30 years. There were a similar proportion of patients with

venous and mixed arterio-venous disease as the cause of ulceration, with similar proportions in each randomised group. Approximately one quarter had no exudate from their wounds, whilst one quarter were considered to have moderate levels of exudate. Most ulcers were considered to have healthy and intact peri-ulcer skin in combination with a number of signs which may be important in ulcer healing. On half of all patients experienced venous eczema, one half had induration and oedema. Ankle brachial pressure index (ABPI) averaged 1.13, though this varied from 0.57 (indicating peripheral arterial disease) to 1.71. In general, the ulcers were small in size with an average area as measured by planimetry of 7.6 cm^2. There was a wide range of ulcer areas from 0.3 to 50.2 cm^2. There was a difference in initial ulcer area between groups in favour of the control group but this did not achieve a standard level of significance. Ulcer pain was present in 60% of patients with relatively few patients experiencing severe pain (6%). The nature of the experienced pain was that it was largely intermittent in nature (85%). The average pain score on a 10 cm visual analogue scale was 3.3, which was similar between groups.

Healing Outcomes.

The primary outcome of this trial was time to complete healing over 12 weeks of follow up on an intention to treat (ITT) basis. *Per protocol* analysis was also undertaken which gave similar results to the ITT and are not shown here.

Table 4 gives the results of the ITT analysis up to 12 weeks. It can be observed that a slightly higher proportion of patients' ulcers healed in the control group compared with the Active group (49.1% versus 44.7%). Most of the remaining ulcers remained unhealed at 12 weeks, though 8% were lost to follow up. Of these, three were adverse events in the Active group, two of which were considered to be related to the dressings used.

Figure 2 gives the Kaplan Meier Failure function. This gives the estimated healing at weekly intervals over the 12 weeks. The active group had slightly better healing over the duration of follow up as observed by the higher curve. The hazard ratio for healing was 1.05.This difference did not approach a standard level of statistical difference (p=0.87). After 4 weeks the estimated healing was 15.2% in the control group compared with 26.8% in the active group. After 12 weeks this had narrowed to 50.2% in the control group compared with 48.4% in the active group. Analysis to 24 weeks saw little change with a hazard ratio of 1.14 with 95% confidence intervals of 0.70 to 1.84, p=0.60.

Further analysis was undertaken to observe the impact of confounding factors on the observed hazard ratio. While most factors were not statistically associated with healing, two factors were identified as independent risk factors for healing. As expected larger ulcers were significantly less likely to achieve healing, whilst the presence of oedema made ulcer healing more likely. This is rather counter-intuitive and requires further investigation. Adjustment for these factors increased the hazard ratio to 1.13 (95%CI 0.64, 2.02), though this still failed to achieve statistical significance (p=0.67).

Quality of Life

Table 5 gives the VLU-QOL scores for the three domains at the three time points, namely, baseline; 12 weeks and 24 weeks. At baseline the scores were similar and at subsequent assessments the scores reduced indicating an improvement in quality of life. The regression analysis showed that over the follow up there was little difference between the active and control group for any of the domains. While perceived pain as assessed by the VA scale reduced during follow up, there was no difference between groups.

Cost and Cost effectiveness

Table 6 gives the cost of products and nurse time over the follow up period to healing, withdrawal or to 12 weeks. The total number of dressing changes was 472 in the 47 patients randomised to active group compared with 782 in the control group. The total cost of care up to the point of healing or withdrawal were £27,853 (mean per patient £525) in the control group compared with £20,507 (mean per patient £436) in the active group. As expected the costs of the primary dressings were higher in the active group compared with the control group at £4,692 versus £2,216, however this cost difference was more than offset by the reduction in nursing time associated with the fewer treatment visits.

In addition to the primary dressings, other dressings were used as secondary dressings. The overall costs were similar between the randomised groups at £233 versus £259 respectively.

Bandages were used to provide compression in these patients. There was a substantially higher cost of bandages in the control group compared with the active group at £3,864 versus £2,597. Hosiery was not costed as these were not

renewed at each dressing change and were used with healed ulcers to prevent re-ulceration.

The cost per healed ulcer was in favour of the active group at £977 compared with £1071 in the control group.

The Markov model results indicated that the total cost of care over the 12 weeks was £28,831 in the control group with a total of 187 ulcer free weeks. For the active group the total cost was £23,801 with 175 ulcer free weeks. The incremental cost (control-active) was £5,031 and the Incremental healed weeks was 12. The cost per additional week healed in the control group was £419.25. This indicates that whilst the control group had slightly better outcome in terms of ulcer free weeks, this came at a substantial extra cost of care implying that there was no advantage in terms of cost effectiveness between groups.

Adverse Events.

Overall there were 26 adverse events recorded in 18 patients. Of these 8 events were recorded in patients in the control group compared with 18 in the active group. In total 7 patients in the control group and 11 patients in the Active group were affected by at least one adverse event. The majority of AEs were related to pain. Of these, only three were considered to be related to the dressing in the Active group versus none in the control group.

Substudy examining Protease Activity

Of the 100 patients randomised 98 had a baseline measure of protease activity. This semi-quantitative method gives a score from zero (no detectable protease activity) to 10 (maximum protease activity). For the purposes of this analysis a score of 5 or over was considered to be high protease activity which could benefit from the use of the test products.

In total, 57/98 (58%) were considered to have high protease activity at baseline. Of these, 29 were in the control group and 28 in the active group. In the control group 13/29 (44.8%) healed compared with 14/28 (50.0%) in the active group. Figure 3 gives the Kaplan Meier failure estimates for these patients with high initial protease

activity. It shows that there was a clear separation between the two randomised groups with the active group having consistently higher healing over the 12 week period. The hazard ratio in this analysis was 1.35, with wide 95% confidence intervals (0.63 to 2.87) p=0.44. Clearly this is a small sample size, though it does indicate the potential for a larger trial to confirm this effect.

The total cost of care on treatment in the control group was £14,979 compared with £11,939 in the active group, with 13 and 14 healed ulcers respectively. The cost per healed ulcer was £1,152.23 in the control group compared with £852.79 in the active group a reduction of 26%.

Using a similar Markov model as before this sub group had a total cost of care over 12 weeks of £14,979 with 92 ulcer free weeks. This compared with a cost of £12,528 and 121 ulcer free weeks in the active group. The incremental cost difference was £2,450 between the control and active group. The incremental weeks healed was -29 weeks. From this it is shown that the active group experienced a higher number of ulcer free weeks but at a lower overall cost. This indicates that the active treatment dominates in this analysis, and therefore provides evidence that the active group was more cost effective than the control treatments.

Discussion

Evidence on the effectiveness of Oxyzyme and Iodozyme is largely limited to *in vitro* studies and case studies. However, a recent review of the literature on Oxyzyme highlighted the evidence from a number of case series in the literature [12]. The Wound Healing Research Institute in Cardiff published a series of 31 patients with chronic venous ulcers [13]. After six weeks using Oxyzyme 32% had healed and 58% had drastically improved. In Toronto 20 patients with ulcers of various aetiologies were followed for four weeks [14]. A total of 18% healed, 68% improved, 5% were static and 9% deteriorated. A larger pilot of 100 patients from 27 European countries with a variety of aetiologies found 10% healed, 63% improved, 16% static and 11% deteriorated after 6 weeks of treatment [15]. Because of the lack of comparative data the present trial was designed to provide information on the introduction of the two products into routine clinical practice by undertaking a randomised controlled trial compared with standard care. This was a preliminary study with sample size set at one hundred patients in total. A formal sample size calculation was not undertaken as there was insufficient evidence on the potential

benefits of using these products on the measured outcomes. It was anticipated that this study would provide such evidence. While inferential statistics were carried out it was not anticipated that a standard level of statistical significance would be achieved in a comparison of randomised groups in either the primary or secondary outcomes that were defined.

In general the protocol was adhered to, though there was evidence that the two active dressings were interchanged on a regular basis in the active group. Moreover, the trial was originally designed to examine the effects in both venous and mixed arterio-venous ulcers. However of the 100 patients randomised only seven had an ankle brachial pressure index of less than 0.8 and so would qualify as a mixed arterio-venous ulcer. This was despite 44 patients being considered as A-V ulcers according to the nurse making the initial assessment.

Those randomised to active treatment performed better in the early stages of treatment with 26.8% healing in the active group compared with 15.2% in the control group up to 4 weeks. However as the study progressed, the graphs became closer indicating a similar healing rate beyond this early stage. This phenomenon is interesting and may benefit from further investigation.

The secondary objectives were to determine the most cost effective method of managing these patients. Whilst the cost of individual dressings in the active treatment group was substantially higher this was more than offset by the increased nursing and other costs caused by patients in the control group being seen more frequently. The average costs were £526 per patient in the control arm compared with £436 in the active arm. With the active arm costing less per healed ulcer at £976 versus £1071. The Incremental cost effectiveness ratio (ICER) indicated that while the control group had marginally better outcomes in terms of ulcer free weeks this was at a much higher cost. This situation is common when introducing new treatments. One might expect a better outcome, but at a higher cost. The situation in this trial is rather unusual in that the test treatment was somewhat cheaper overall, but provided a slightly poorer outcome. However, when only patients with high protease activity were analysed there was a clear difference in cost effectiveness both in terms of cost per healed ulcer, but also in terms of cost of ulcer free weeks in which the active group dominated. This indicates that the active group provided a better outcome at a lower cost. While it has to be acknowledged that the high PA group was not strictly randomised in that they were a subset of the main

trial, this does provide compelling evidence of the potential for cost effectiveness using these new dressings.

In terms of the patient related outcomes while there was good evidence of an improvement in health related quality of life in patients on treatment, there was little difference between the two randomised groups. This is consistent with a number of trials that have been undertaken in relation to the healing of venous ulcers using different bandage and dressing combinations [16,17].

The British National Formulary (BNF) identifies seven wound care products in its section on protease modulating matrix dressings [10]. It does however give the caveat that *"Protease-modulating matrix dressings alter the activity of* proteolytic enzymes *in chronic wounds; the clinical significance of this approach is yet to be demonstrated".* Recent work has examined the potential for protease modifying products. A small randomised trial (n=75) examined how the wound bed preparation was altered by the use of a protease modulating hydrogel in patients with venous ulcers [18]. After 14 days there was evidence of significant reduction in fibrin and necrotic tissue and increase in granulation tissue in the actively treated group compared with a control hydrogel. Moreover, a study of compression therapy indicated that protease activity decreased following compression therapy, with reductions in certain MMPs associated with higher healing at 4 weeks [19].

Evidence from randomised clinical trials has been limited in patients with venous ulceration. In 2002 Vin *et al* published the results of a trial of 73 patients randomised to either collagen and oxidised regenerated cellulose (ORC) dressing (Promogran) or non-adherent dressing [20]. Their conclusion was that 20% more wounds healed or improved over the 12 week follow up which just failed to achieve a standard level of statistical significance (p=0.0797). In a smaller trial of 30 patients with follow up to two weeks using the same active therapy versus 10 patients using moist wound healing, the authors concluded that there was improved quality of healing and pain levels which occurred as early as one week after starting the therapy [21]. The only large trial of this nature was undertaken in diabetic patients comparing ORC with saline gauze as a control dressing [22]. This failed to demonstrate a significant difference between the randomised groups in the 271 patients entered into this trial.

Despite the lack of evidence from appropriate randomised controlled trials the present study gives some indication of how protease inhibitory dressings have the

potential for improving healing in patients with high initial protease activity. Those patients in the active group have shifted their healing graph to the left (figure 2), indicating a quicker response to healing compared with the control group, though the study was not of sufficient size to demonstrate statistical significance. Healing would appear to occur on average 1-2 weeks sooner than in the control group over the 12 week period. At the end of 12 weeks the healing rates were 51% and 45% respectively.

In conclusion, the results of the present study provide some useful information on the potential for the treatment of patients with high protease activity. It also indicates that there is a good cost effectiveness argument in favour of using higher cost dressings if this provides a longer wear time, and less frequent visits for treatment. Clearly, more evidence is needed to confirm these results.

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SECTION 8 : REFERENCES

1.Moffatt CJ, Franks PJ, Doherty DC, Martin R, Blewett R, Ross F Prevalence of leg ulceration: a study in a London population. *QJM* 2004; 97(7): 431-437

2. Posnett J, Franks PJ. The burden of chronic wounds in the UK. *Nurs Times.* 2008; 104 (3):44-5.

3.Cullum N, Nelson EA, Fletcher AW, Sheldon TA.
Compression for venous leg ulcers.
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000265.pub3

4.Moffatt CJ (2003), Understanding compression therapy. In EWMA Position Document. Understanding compression therapy. London. Medical Education Partnership.

5. Moher D, Schulz KF, Altman DG; CONSORT GROUP (Consolidated Standards of Reporting Trials).The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Ann Intern Med.* 2001; 134(8):657-62

6. Boykin JV. The nitric oxide connection :hyperbaric oxygen therapy, becaplermin and diabetic ulcer management. *Advanced Skin Wound Care*. 2000; 13 (4 Part 1):169-174

7. Gottrup F. Oxygen in wound healing and infection. *World Journal of Surgery* 2004; 28 (3) 312- 315

8. Hareendran A, Doll H, Wild DJ, Moffatt CJ, Musgrove E, Wheatley C, Franks PJ. The Venous Leg Ulcer Quality of Life (VLU-QoL) questionnaire: Development and Psychometric Validation. *Wound Repair & Regeneration* 2007*:*15(4); 465-473

9. Melzack R (1987) The short form McGill pain questionnaire. *Pain* **30**:191-7

10. British National Formulary (BNF). www.bnf.org

11. Curtis L. Unit costs of Health & Social Care 2011. Personal Social Services Research Unit, University of Kent. 2011

12. Brimson CH, Nigam Y
The role of oxygen-associated therapies for the healing of chronic wounds, particularly in patients with diabetes. *Journal of the European Academy of Dermatology and Venereology* 2013; 27: 411-418

13.Ivins N, Simmonds W, Turner A, Harding K. The use of an oxygenating hydrogel dressing in VLU. *Wounds UK* 2007; 3(1) 77-81

14. Queen D, Coutts P, Fierheller M, Sibbald RG. The Use of a Novel Oxygenating Hydrogel Dressing in the Treatment of Different Chronic Wounds *Advancs in Skin and Wound Care* 2007; 20(4) 200-206

15.Davis P, Wood L Wood Z, Eaton A, Wilkins J. Clinical experience with a glucose oxidase-containing dressing on recalcitrant wounds. *Journal of Wound Care* 2009; 18(3) 114-121

16. Franks PJ, Bosanquet N, Brown D, Straub J, Harper DR, Ruckley CV. Perceived health in a randomised trial of treatment for chronic venous ulceration. *Eur. J. Vasc. Endovasc. Surg.* 1999; 17 (2): 155-159

17. Franks PJ, Moody M, Moffatt CJ, Patton J, Bradley L, Chaloner D, Stevens J, Stevens J, Lewis C. Quality of life in a trial of short stretch versus four layer bandaging in the management of chronic venous ulceration. *Phlebology* 2004;19 (2): 87-91

18. Humbert P, Faivre B, Veran Y et al On behalf of the CLEANSITE study group. Protease-modulating polyacrylate-based hydrogel stimulates wound bed preparation in venous leg ulcers – a randomized controlled trial. *JEADV* 2014; Doi DOI: 10.1111/jdv.12400

19. Beidler SK, Douillet CD, Berndt DF, Keagy BA, Rich PB, Marston WA. Multiplexed analysis of matrix metalloproteinases in leg ulcer tissue of patients with chronic venous insufficiency before and after compression therapy. *Wound Repair & Regeneration* 2008; 16: 642-648

20. Vin S, Teot L, Meaume S. The healing properties of PROMOGRAN in venous leg ulcers. *J. Wound Care* 2002; 11(9): 335-41.

21. Wollina U, Schmidt WD, Kronert C et al. Some effets of topical collagen-based matrix on the microcirculation and wound healing in patients with chronic venous leg ulcers: preliminary observations. *Int J Low Extrem Wounds* 2005; 4(4): 214-24.

22. Veves A, Sheehan P, Pharm HT. A randomised controlled trial of Promogran (a collagen/oxidised regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. *Arch. Surg*. 2002; 137(7) 822-7

Table 1. Basic Demographic Information and Allied Health Problems						
	Control		**Active**		**Total**	
	N=53		**N=47**		**N=100**	
Age (years)						
Mean	69.4		69.7		69.5	
Standard deviation	13.5		13.2		13.3	
Minimum	31.3		39.3		31.3	
Maximum	91.4		92.5		92.5	
Count	53		46		99	
	N	**Percent**	**N**	**Percent**	**N**	**Percent**
Gender						
Male	29	54.7	23	48.9	52	52.0
Female	24	45.3	24	51.1	48	48.0
Total	53		47		100	100.0
Diabetes						
Yes	8	15.1	6	12.8	14	14.0
No	45	84.9	41	87.2	86	86.0
Total	53		47		100	100.0
Diabetes Type						
I	0	0	3	50.0	3	21.4
II	8	100.0	3	50.0	11	78.6
Method of control						
Insulin	2	25.0	3	50.0	5	35.7
Non-insulin	6	75.0	3	50.0	9	64.3
Rheumatoid Arthritis						
Yes	7	13.2	4	8.5	11	11.0
No	46	86.8	43	91.5	89	89.0
Total	53		47		100	10
Smoker						
Yes	6	11.3	6	12.8	12	12.0
No	47	88.7	41	87.2	88	88.0
Total	53		47		100	100.0
Hypertension						
Yes	25	47.2	17	36.2	42	42.0
No	28	52.8	30	63.8	58	58.0
Total	53		47		100	100.0

Table 2. Factors Related to Venous and Cardiovascular Disease						
	Control		**Active**		**Total**	
	N	**Percent**	**N**	**Percent**	**N**	**Percent**
Varicose veins						
Yes	33	62.3	37	78.7	70	70.0
No	20	37.7	10	21.3	30	30.0
Total	53		47		100	100.0
Varicose vein surgery						
Yes	13	24.5	17	36.2	30	30.0
No	40	75.5	30	63.8	70	70.0
Total	53		47		100	100.0
History of Deep vein thrombosis						
Yes	6	11.3	7	14.9	13	13.0
No	47	88.7	40	85.1	87	87.0
Total	53		47		100	100.0
History of pulmonary embolism						
Yes	2	3.8	0	0	2	2.0
No	51	96.2	47	100.0	98	98.0
Total	53		47		100	100.0
History of myocardial infarction						
Yes	5	10.4	1	2.1	6	6.0
No	48	89.6	46	97.9	94	94.0
Total	53		47		100	100.0
History of stroke						
Yes	2	3.8	3	6.4	5	5.0
No	51	96.2	44	93.6	95	95.0
Total	53		47		100	100.0
History of Transient Ischaemic Attack (TIA)						
Yes	1	1.9	1	2.1	2	2.0
No	52	98.1	46	97.8	98	98.0
Total	53		47		100	100.0
Arterial leg surgery						
Yes	3	5.7	1	2.1	4	4.0
No	50	94.3	46	97.9	96	96.0
Total	53		47		100	100.0
Angioplasty						
Yes	1	1.9	0	0	1	1.0
No	52	98.1	47	100.0	99	99.0
Total	53		47		100	100.0

Table 3. Ulcer Details						
	Control		**Active**		**Total**	
	N	**Percent**	**N**	**Percent**	**N**	**Percent**
Side						
Right	22	41.5	22	47.8	44	44.4
Left	31	58.5	24	52.2	55	55.6
	53		46		99	
Episodes						
First	19	35.8	17	36.2	36	36.0
One previous	16	30.2	9	19.1	25	25.0
2-5 episodes	11	20.8	14	29.8	25	25.0
>5 episodes	7	13.2	7	14.9	14	14.0
Total	53		47		100	100.0
Ulcer present on contralateral limb						
Yes	5	9.4	8	17.0	13	13.0
No	48	90.6	39	83.0	87	87.0
Total	53		47		100	100.0
Ulcer position on leg *						
Medial malleolus	22	41.5	17	36.2	39	39.0
Lateral malleolus	10	18.9	10	21.3	20	20.0
Tibial crest	11	20.8	8	17.0	19	19.0
Calf	5	9.4	6	12.8	11	11.0
Other	7	13.2	9	19.1	16	16.0
Total	55		50		105	
Ulcer Duration (months)						
mean	20.0		17.6		18.9	
SD	56.5		40.3		49.5	
Ulcer aetiology						
Venous	30	56.6	26	55.3	56	56.0
Mixed A-V	23	43.4	21	44.7	44	44.0
Total	53		47		100	100.0
Level of exudate						
None	13	25.0	13	28.2	26	26.5
Low	23	44.2	24	52.2	47	48.0
Moderate	16	30.8	9	19.6	25	25.5
	52		46		98	
Peri-wound skin**						
Healthy & Intact	39	73.6	33	70.2	72	72.0
Varicose eczema	26	49.1	25	53.2	51	51.0
Hard Induration	25	47.2	29	61.7	54	54.0
Oedema	26	49.1	22	46.8	48	48.0
Maceration	9	17.0	5	10.6	14	14.0
Other	2	3.8	1	2.1	3	3.0
Ankle Brachial Pressure Index						
Mean	1.12		1.14		1.13	
SD	0.21		0.24		0.23	
Wound Area Measurement (cm^2)						
Mean	7.1		8.1		7.6	
SD	10.0		10.2		10.1	

Table 3 (continued)

Ulcer pain						
Present	33	62.3	27	57.4	60	60.0
Absent	20	37.7	20	42.6	40	40.0
Total	53		47		100	100.0
None	20	37.7	20	42.6	40	40.0
Mild	11	20.8	10	21.3	21	21.0
Moderate	18	34.0	15	31.9	33	33.0
Severe	4	7.5	2	4.3	6	6.0
Total	53		47		100	100.0
Continuous	4	12.1	5	19.2	9	15.3
Intermittent	29	87.9	21	80.8	50	84.7
Total	33		26		59	100.0
VA-pain						
Mean	3.4		3.3		3.3	
SD	3.5		3.4		3.5	

*ulcer position may have been on more than one location
**patients may have had more than one description of the peri-ulcer skin

Table 4. Intention to Treat Healing Outcomes and Reasons for Withdrawal up to 12 weeks						
	Control		**Active**		**Total**	
	N	**Percent**	**N**	**Percent**	**N**	**Percent**
Healed	26	49.1	21	44.7	47	47.0
Unhealed	25	47.2	20	42.6	45	45.0
Lost to follow up	2	3.8	6	12.8	8	8.0
Reason						100.0
	142: Patient withdrew as preferred the Active dressings		114:AE: Hospitalised chest pain			
	176: Administrative: incomplete		116: AE: Pain			
			121: Administrative: incomplete			
			137: Patient diagnosed with thyroid disease			
			150: Wound static ?fungating carcinoma			
			225: AE: Pain & discomfort			

Table 5. Health Related Quality of Life at different time points						
	Control		**Active**		**Difference (95%CI)**	**p-value**
	n		n			
Activities						
Baseline	53	39.6 (26.8)	46	40.0 (25.3)		
12 weeks	49	31.3 (24.9)	38	28.8 (25.8)	0.04 (-10.2,10.3)	0.99
24 weeks	45	25.3 (27.9)	39	23.1 (23.3)		
Psychological						
Baseline	51	41.5 (28.9)	46	46.7 (28.1)		
12 weeks	49	32.4 (27.2)	39	36.9 (26.7)	4.8 (-6.2,15.8)	0.40
24 weeks	45	27.0 (27.4)	38	28.3 (28.1)		
Symptom distress						
Baseline	51	42.5 (24.4)	45	46.4(21.4)		
12 weeks	49	32.6 (22.4)	39	36.1 (25.4)	3.9 (-5.9,13.6)	0.44
24 weeks	46	23.5 (26.2)	37	26.1 (27.7)		

Table 6. Costing Analysis for Dressings, Bandages and Nursing Time						
	Control		**Active**		**Total**	
N	53		47		100	
Visits for treatment						
Mean	14.8		10.04		12.54	
Total visits	782		472		1254	
Primary dressing costs (£)						
Mean	41.83		99.84		69.09	
Total Cost	2216.74		4692.32		6909.06	
Secondary dressing costs (£)						
Mean	4.90		4.96		4.93	
Total Cost	259.56		233.24		492.80	
Bandage Costs (£)						
Mean	72.91		55.26		64.61	
Total cost	3864.37		2597.09		6461.46	
Dressing Packs (£)						
Mean	7.52		5.12		63.95	
Total cost	398.82		240.72		639.54	
Staffing costs @ £27 per visit						
Mean	398.38		271.15		338.58	
Total Cost	21114.00		12744.00		33858.00	
Total cost of dressings, Bandages & Nursing time						
Mean	525.54		436.33		483.61	
Total cost	27853.49		20507.37		48360.86	
Number healed	26		21		47	
Cost per healed ulcer	1071.29		976.54		1028.95	

Figure 1. Trial Flow Diagram

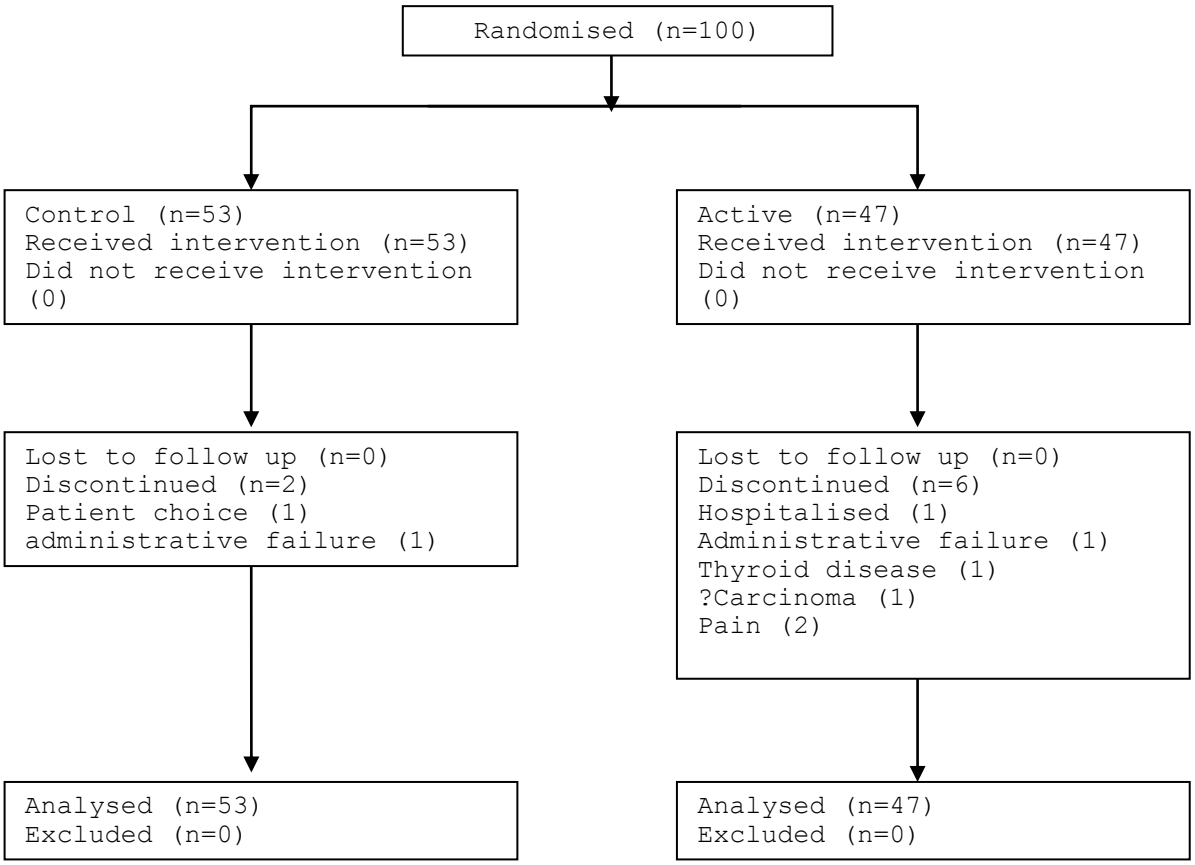
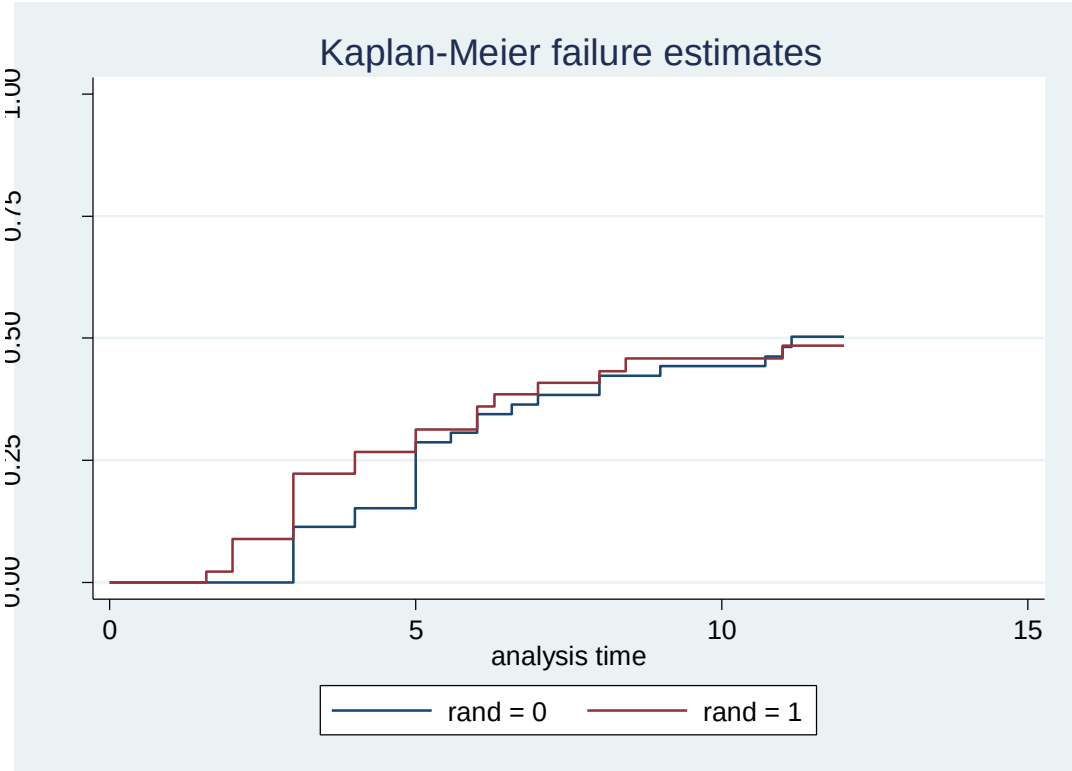
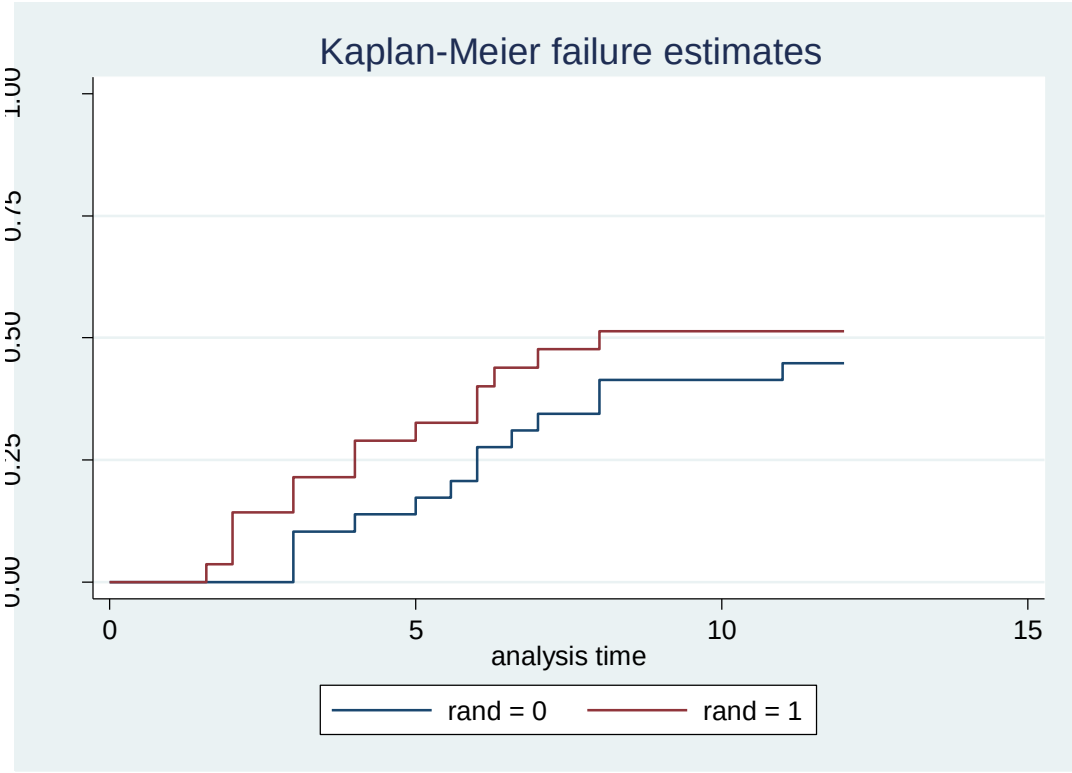


Figure 2. Kaplan Meier Failure Estimates over 12 weeks given by Randomised Groups



Hazard Ratio =1.13, (95%CI 0.64 to 2.02), p=0.67.

Figure 3. Kaplan Meier Failure Estimates over 12 weeks for Patients with high Protease Activity given by Randomised Groups



Hazard Ratio =1.35, (95%CI 0.63 to 2.87), p=0.44.